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CORRESPONDENCE

Skin necrosis complicated by warfarin-induced protein S deficiency

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Warfarin is a widely and easily administered oral anticoagulant and becomes the standard treatment for various thromboembolic events including livedo vasculitis.[1]

A healthy 15-year-old girl presented with multiple progressive painful ulcers and atrophie blanche over bilateral lower legs and feet for 4 months (Fig. 1A). Skin biopsy revealed hyalinized vascular change and thrombosis of the upper reticular dermal vessels (Fig. 1B). Direct immunofluorescence study revealed perivascular fibrinogen deposition. A diagnosis of livedo vasculitis was made.

Warfarin (1.65 mg/day) was administered to control the disease activity. However, clinical symptoms and signs did not improve but exacerbate with extensive skin necrosis 2 weeks later (Fig. 1C). Histopathologic examination of the necrotic area showed diffuse thrombotic vasculopathies in the upper dermis (Fig. 1D). Prothrombin time was prolonged to 14.8 seconds (control: 10.7 seconds) and the international normalized ratio was 1.47. Partial thromboplastin time was 28.8 seconds (control: 27.1 seconds). Elevation of D–dimer (0.6 mg/L, normal range: <0.55 mg/L) was noted. A deficiency of protein S (29% activity, normal range: 55%–130%) was identified without evidence for a deficiency of protein C (105% activity, normal range: 80%–132%). Antithrombin III, fibrinogen, clotting factors (VIII, IX, XI), and von Willebrand factor were all within normal ranges. Serum homocysteine was not elevated and cryoglobulin was negative. Survey of the autoimmune antibodies showed negative results. Serum immunoglobulin G, immunoglobulin A, immunoglobulin M, complement 3, complement 4, C-reactive protein, complete blood count, erythrocyte sedimentation rate, liver function, renal function, electrolytes, electrocardiography, stool, and urine examinations were all normal. Parents and siblings of the patient were tested for serum protein C and protein S, which turned out to be normal.

Warfarin was discontinued and the patient was treated by subcutaneous injections of enoxaparin sodium (60 mg/day) for 2 weeks. Pain improved without progression of skin necrosis and prothrombin time (10.7 seconds, control: 11.3 seconds), D–dimer (0.36 mg/L), and serum protein S level (74% activity) all became normal. The skin lesions gradually healed within 1 month.

Warfarin-induced skin necrosis is a rare complication which affects 0.01%–0.1% of all patients treated with oral anticoagulants.[2] A number of cases have been reported in association with congenital deficiency of protein C or protein S.[3] Some other cases are related to acquired protein C and protein S deficiency.[4] Isolated

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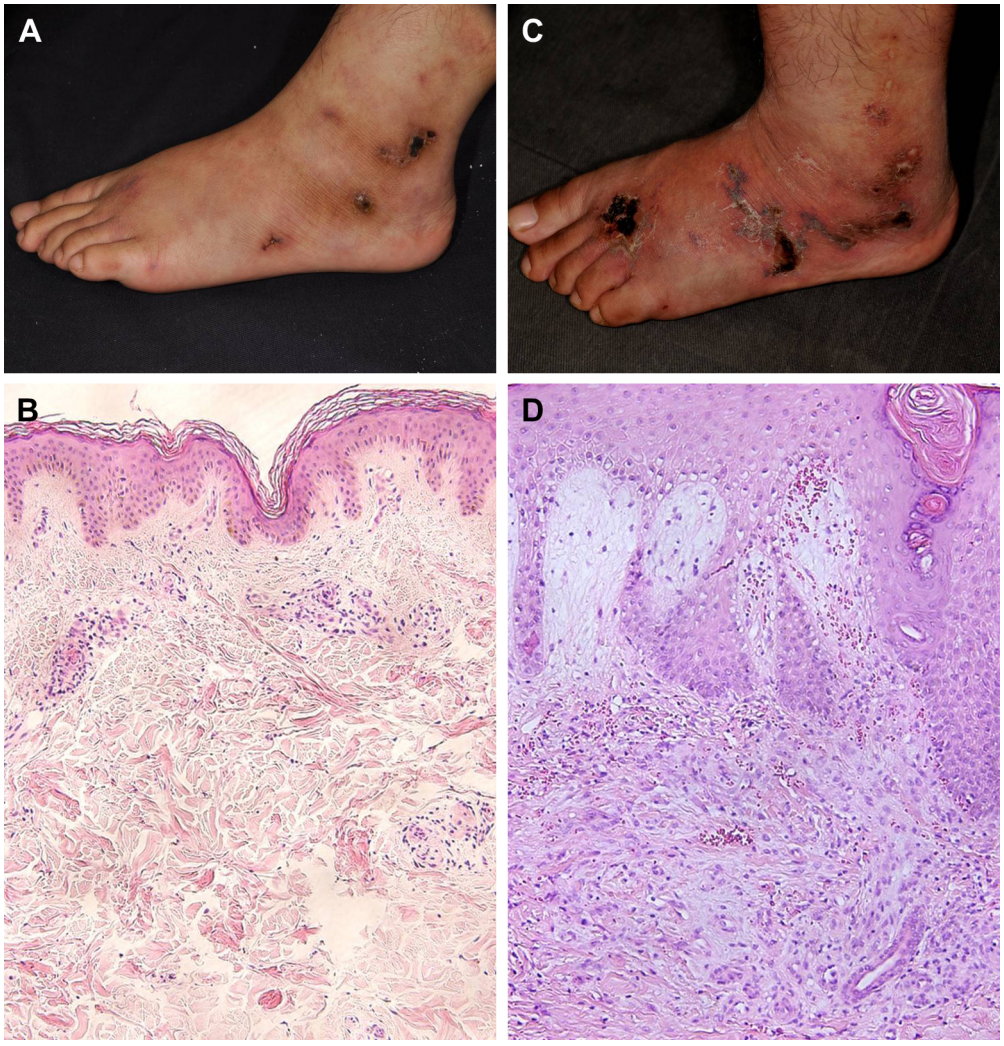

Figure 1 (A) Painful crusted ulcers and atrophie blanche on the patient's left ankle and foot. Similar lesions could be observed in the opposite lower extremity. (B) Hyalinization and thrombosis of the upper reticular dermal vessels. Minimal perivascular lymphocytic infiltrate was noted (hematoxylin and eosin, 100×). (C) Extensive necrotic areas were noted on the patient's left dorsal foot 2 weeks later after administration of warfarin. The patient's right lower leg and foot also showed similar skin necrosis. (D) Thrombotic vasculopathy with fibrinoid necrosis of the vascular wall and marked red blood cell extravasation in the upper dermis. Prominent papillary dermal edema, interstitial, and perivascular lymphocytic infiltration could also be noted (hematoxylin and eosin, 100×).

acquired protein S deficiency has never been reported. The pathomechanism of this adverse cutaneous reaction is not fully understood and had been mainly explained by the rapid decline of serum protein C level relative to coagulation factors II, IX, and X in the initial stages of warfarin action.[5] Here, we first report that warfarin can selectively induce protein S deficiency and low-molecular-weight heparin can be used to prevent further thrombosis. We recommend that close monitoring of serum protein S and protein C levels within the first 2 weeks in patients under warfarin treatment is warranted. Clinicians should be alert to this rare, but potentially serious, complication whenever suspicious skin lesions occur. Early diagnosis and drug withdrawal can be limb or life saving.

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